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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
HABTE, KAHSAY

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 04/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/026,966	BEBBINGTON ET AL.	
	Examiner	Art Unit	
	Kahsay Habte, Ph. D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *14,17,20 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,15,16,18,19 and 22-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2&3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Restriction/Election

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-13 (in part), 15-16 (in part), 18-19 (in part) and 22-29 (in part), drawn to pyrimidines ($Z^1 = Z^2 = N$), classified in class 544, and subclass various.

II. Claims 1 -13 (in part), 15-16 (in part), 18-19 (in part) and 22-29 (in part), drawn pyridines (either Z^1 or Z^2 is N) classified in class 546, and subclass various.

III. Claims 14, 17 and 20-21, drawn to complex composition, classified in class 514, and subclass various.

The inventions are distinct, each from the other because of the following reasons: Groups I-II are directed to structurally dissimilar compounds such that the variable core created by the varying definitions of Z^1 and Z^2 in formula **IV** and core structures do not belong to the same recognized class of chemical compounds in the art, and references anticipating one invention, would not render obvious the others. For example, Group I that is drawn to pyrimidines is different from Groups II and III, since it contains 2 nitrogens in a six membered ring. Group II is drawn to pyridine ring (one nitrogen in a six-membered ring) and this feature is not present in Groups I or II. Group III is drawn to complex composition and is different from Groups I and II, because Groups I and II are drawn to simple composition and contain no additional ingredient. Group III has an

additional ingredient (chemotherapeutic agent) that is not present in Groups I and II. This is because of the possibility of synergistic interaction, which is usually the purpose of the complex composition in the first place. Group I-III are directed to group of compounds that have different composition and do not belong to the same recognized class of chemical compounds in the art, and references anticipating one invention, would not render obvious the others. Thus, separate searches in the literature as well as in the U.S. Patent Classification System would be required. Each group's compounds are made and used independently of each other and could support separate patents. The compounds differ significantly in chemical structures. One skilled in the art would not consider such diverse structure equivalents of each other.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions anticipated by prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Because these inventions are distinct for the reasons given above and have acquired separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

During a telephone conversation with Ms. Andrea Robidoux on March 24, 2003 a provisional election was made without traverse to prosecute the invention of Group I, claim 1-13, 15-16, 18-19, and 22-29. Affirmation of this election must be made by

applicant in replying to this Office action. Claims 14, 17 and 20-21 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Objection

2. Claims 1-13, 15-16, 18-19 and 22-29 are drawn to multiple inventions for reasons set forth in the restriction requirement. The claims are examined only to the extent that they read on the elected invention. Cancellation of the non-elected subject matter is recommended in response to this Office Action.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1-6,13-16, 18-19 and 22-29 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-30 of copending Application No.10/027,001. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 is generic to claim 1 that is recited in Application No.10/027,001. That is claim 1 of Application No.10/027,001 falls entirely within the scope of claim 1, or in other words, claim 1 is anticipated by claim 1 of copending Application No.10/027,001. Specifically, the compounds of copending Application No.10/027,001 in formula IIa are the same as the compounds of claim 1 when applicant's formula IV is Q = S and Z1=Z2 = N. For example, many species that are the same as of copending Application No.10/027,001 are disclosed on Table 1 (pages 45-51) when Z1=Z2=N and Q= S.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-25 are ejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to

make and/or use the invention. There has been recited a method of treating Alzheimer's disease, but the specification is not enabled.

A number of factors are relevant to whether undue experimentation would be required to practice the claimed invention, including "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

(1). Breadth of Claims:

Scope of Compounds - The scope of the compounds is broad. It is apparent that hundreds of millions of combinations of compounds can be created from the definitions, owing especially to broad scope of $R^{2'}$, R^2, R^x, R^y, R^1 and Q.

(2). Direction of Guidance: The amount of direction or guidance is minimal. The dosage range is 10,000 fold and hence largely useless. The dosage is completely generic; it is the same regardless of which disorder is being treated.

(3). State of Prior Art: There is no evidence of record that compounds structurally similar to these pyrimidine derivative compounds are in use for the treatment of Alzheimer's disease.

(4). Working Examples: There is no any working example that indicates the inhibition of GSK-3, which in return is presumed to treat AD. There is no data for any actual treatment of Alzheimer's disease or of any animal model for the treatment of Alzheimer's disease.

(5). Nature of the Invention and Predictability: It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(6). The Relative Skill of Those in the Art: Applicants claim a method of treatment for AD, this is a very hard to treat disease. The central characteristic of Alzheimer's disease is the deficiency in the level of the neurotransmitter Acetylcholine that plays an important role in memory. Alzheimer's Disease is an extraordinarily difficult disease to treat, and has been the subject of a vast amount of research. Despite an enormous number of different approaches, the skill level in the art is so low relative to the difficulty of task that the only success has come from treatment by compounds which are

Acetylcholinesterase inhibitors (Aricept®, Cognex®, Exelon®, and Reminyl®) a property these compounds are not disclosed to have.

According to a review article by Philip Cohen and Sheelagh Frame (Nature Reviews/ Molecular Cell Biology, Vol. 2, pages 769-776, October 2001), the authors on page 775 concluded "However, our knowledge of the biological roles of GSK-3 is still in its infancy, and much further experimentation is still necessary, exploiting the improved that are gradually becoming available. The development of increasingly potent and specific inhibitors of GSK-3, as will the availability of mice that lack either one or both GSK3 isoforms." This indicates that the skill level in this art is too low and that the study of GSK3 is at its early stage.

It is also noted that GSK has two isoforms- GSK-3α and GSK-3β (note Figure 4 of Cohen). Note that Cohen discusses almost entirely the β; little is known about the α. Which isoform is being referred by applicants? There is no guidance in the specification to link any of the isoforms with Alzheimer's disease. The skill level in the art is too low. As the authors indicate in the conclusion "the role of GSK-3 in many different cellular processes in which it is currently implicated will continually have to be critically reviewed, as new pharmacological and genetic tools become available." This clearly shows that the study to understand GSK-3 kinases, is in its very early stage.

In regard to the treatment of Alzheimer's disease, the review article on page 774 (box 4) concludes "The microtubule-associated protein Tau, which is thought to stabilize microtubules *in vivo* and to promote their polymerization, is phosphorylated relatively high levels in fetal brain and the brains of newborn animals, but at much lower levels in

adult brain. However, in Alzheimer's disease and several other neurodegenerative diseases, Tau is found in an abnormally hyperphosphorylated, filamentous and insoluble form. Such hyperphosphorylation is believed to be an early event that precedes its assembly into filaments. Whether hyperphosphorylation is necessary or sufficient for filament assembly is unclear;.....These observations raise the possibily that GSK-3 inhibitors might reduce the hyperphosphorylation of Tau, thereby enhancing its interaction with microtubules and reducing the pool of Tau available for aberrant assembly" emphasis added. This indicates that the inhibition of GSK-3 for the treatment of Alzheimer's disease is in its infancy stage. As concluded by the authors, it is just an observation that a treatment of Alzheimer's disease might be treated by inhibiting GSK-3 that are responsible for abnormal hyperphosphorylation Tau. It is no more than a suggestion. To this day it is unclear, if inhibition of GSK-3 is useful for the treatment of Alzheimer's disease.

(7). The Quantity of Experimentation Necessary: Immense, especially in view of point 6, since the inhibition of GSK-3 for the treatment of AD has never been accomplished or even researched. Thus, no guidance from the success of others is available from this experimentation.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*,

999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-13,15-16, 18-19 and 22-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention:

a. Claims 1 and claims dependent thereon are rejected because the term "Heterocyclyl" is indefinite. What is the number and nature of the heteroatoms? Can the ring be fused or spiroconnected to another ring, and if so, what kind of ring? Can the ring be bridged? Unsaturated? Cf *In re Wiggins*, 179 USPQ 421, 423.

b. In claim 37, the abbreviation "AML" is incorrect. It should read as "ALS."

c. Claims 18 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claims 18 and 24 there has been recited a method of treating an aurora-2 or GSK-3-mediated diseases. The scope of claims 18

and 24 are unknown. Which diseases are these? Determining whether a given disease responds or does not respond to such inhibitor will surely involve undue experimentation. Suppose that a given inhibitor X when administered to a patient with Disease D does not obtain a response. Does one then conclude that Disease D does not fall within this claim? Keep in mind that:

A. It may be that the next patient will respond. It is quite common for pharmaceuticals to work only with some people, not all. Thus, how many need to be tested?

B. It may be that the wrong dosage or dosage regimen was employed. It is quite common for pharmaceuticals to work at one dosage, but not at another, which is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? Thus, how many dosages and dosage regimens must be tried before one is certain that this pharmaceutical won't affect Disease D?

C. It may be that X simply isn't potent enough for Disease D, but that another inhibitor Y is potent enough, so that D really does fall within the claim. Thus, how many different mediators must be tried before one concludes that D doesn't fall within the claim?

D. Conversely, if D responds to Y but not to X, can one really conclude that D falls within the claim? It may be that the X result is giving the accurate answer, and that the success of Y arises from some other unknown property, which Y is capable of.

Thus, when mixed results are obtained, how many more pharmaceuticals need be tested?

E. Finally, suppose that X really will work, but only when combined with Z. There are for example, agents in the antiviral and anticancer technology, which are not themselves effective, but the disease will respond when the agents are combined with something else.

F. In addition, literally speaking, any disorder can be treated with any drug, although the treatment might not be successful. Assuming that "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000?

As a result, determining the true scope of the claim will involve extensive and potentially open-ended research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte, Ph. D. whose telephone number is (703) 308-4717. The examiner can normally be reached on M-F (9.00AM- 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 703-308-4716. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Kahsay Habte, Ph. D.
Examiner
Art Unit 1624

Mark L. Berch
Primary Examiner
Art Unit 1624

KH
March 31, 2003